REMARKS

Claims 1-4, 6-8, 10-18, 34-39, and 64-132 were pending. Claims 75, 85, 97, 107, 119, and 129 have been cancelled. Claims 6, 64, 76, 86, 98, 108, 115, 120, 130, and 132 have been amended. Therefore, claims 1-4, 6-8, 10-18, 34-39, 64-74, 76-84, 86-96, 98-106, 108-118, 120-128, and 130-132, will be pending upon entry of the instant amendment.

Claims 6, 64, 76, 86, 98, 108, 115, 120, 130, and 132 have been amended to clarify the invention. Support for amendments to the claims can be found, for example, at least in the claims as originally pending and in the specification as originally filed, for example, at least at page 3, line 22 through page 4, line 13.

Rejection of Claims 1-4, 6-8, 34-39, 75 and 84-132 under 35 U.S.C. § 112, first paragraph

Claims 1-4, 6-8, 34-39, 75, and 84-132 are rejected under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for a limited set of nervous system diseases such as those having undesired neuronal activity, e.g., multiple sclerosis and Parkinson's disease, does not reasonably provide enablement for claimed conditions such as fungal infections and aging."

Applicants note that claims 1-4 and 6-8 are directed to a method for increasing ATP production of a subject, comprising administering to said subject an effective amount of a creatine compound and an ATP enhancing agent.

Applicants note that claims 34-39 are directed to a method of protecting the nervous system of a subject against oxidative damage, comprising administering to said subject an effective amount of a creatine compound and a neuroprotective agent.

Applicants note that these claims are not directed to treating nervous system diseases but rather to increasing ATP production and protecting the nervous system of a subject. Applicants submit that the application is enabling for methods of increasing ATP production and protecting the nervous system of a subject. For example, in the specification at least at page 43, line 38 through page 44, line 22, the specification describes assays and examples which can be used to test sustained ATP production. Furthermore, the specification at page 53, line 17-26, describes a method for testing the ability of creatine compounds to provide neuroprotection. Therefore, Applicants submit that the specification is enabling for methods of increasing ATP production and protection of the nervous system.

Applicants note that claims 86-107 are directed to a method for treating Parkinson's disease. Claims 108-129 are directed to a method for treating Huntington's disease. Applicants also note that claims 130 and 131 are directed to a pharmaceutical composition for the treatment of amyotrophic lateral sclerosis, Huntington's disease or Parkinson's disease. Finally, Applicants note that claim 132 is a packaged nervous system disease composition for the treatment of amyotrophic lateral sclerosis, Parkinson's disease or Huntington's disease.

The claims as currently amended are directed to the treatment of amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease, each of which was indicated by the Examiner as being enabled in the present Office Action (e.g., "the specification, while being enabling for treatment of specific nervous system disease, (as demonstrated by the Examples 1-3...illustrating models for Huntington's disease, Parkinson's disease, ALS disease) comprising the administration of creatine compounds."). Therefore, Applicants submit that the present application is enabling for methods and pharmaceutical compositions for the treatment of amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.

Therefore, Applicants respectfully request that this rejection of claims 1-4, 6-8, 34-39, 75, and 84-132 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejection of Claims 6, 57, 84, 85, 97, 106, 107, 119, 128, 129, 130 and 132 under 35 U.S.C. § 112, first paragraph

The Examiner found "the terms 'nervous system disease,' 'vitamin' [in] claims 6, 57, 85, 97, 107, 119, 'prevention' [in] claim 107, 'modulating' [in] claim 132, 'human' claims 84, 106, 128, 'approved drugs' [in] claim 129 [to be] too indefinite to the extent they read on inoperative subject matter."

Claims 6, 85, and 107 no longer recite the term "vitamin(s)." Claims 57, 97 and 119 have been cancelled, thus rendering their rejections moot.

Claim 107 no longer recites the term "prevention." Claim 129 no longer recites the term "approved drugs." Claims 130 and 132 no longer recite the word "modulating" or "modulator."

Applicants submit that the term "human" is a term well known in the art. One of ordinary skill in the art would have understood what Applicants meant by the term "human" at the time the application was filed. Applicants request clarification about how the term "human" is indefinite.

Therefore, Applicants request that this rejection of claims 57, 84, 97, 106, 119, 128, 129 and 132 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejection of Claims 1-4, 6-8, 34-39, 75 and 84-132 under 35 U.S.C. § 103(a)

Claims 1-4, 6-8, 34-39, 75 and 84-132 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hagenfeldt *et al.*, Applicants' admission in the present specification, and Schultheiss *et al.* (*J. Neurochemistry*, June, 1990, 54(6), 1858-63) (hereinafter "Schultheiss *et al.*").

Applicants claim methods of increasing ATP production of a subject, by administering to the subject an effective amount of a creatine compound and an ATP enhancing agent. Applicants also claim methods of protecting a subject against oxidative damage, by administering to the subject an effective amount of a creatine compound and a neuroprotective agent. In addition, Applicants also claim methods and compositions for the treatment of amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease in a subject. The methods include administering to a subject a therapeutically effective amount of a combination of creatine, creatine phosphate or a creatine analog and a neuroprotective agent. The neuroprotective agent is selected from the group consisting of inhibitors of glutamate excitotoxicity, mitochondrial cofactors, electron transport chain regulators, spin traps, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcysteine, antioxidants, lipoic acid, cofactors, riboflavin, and CoQ10.

Hagenfeldt *et al.* discusses the results of a clinical experiment of administering creatine to a MELAS patient. It was found that the patient had improved muscle function and fewer headaches after three months of creatine administration. Hagenfeldt *et al.* does not teach or suggest methods involving the administration of creatine in combination with a neuroprotective agent. Hagenfeldt *et al.* fails to teach or suggest a method for increasing ATP production. Hagenfeldt *et al.* also fails to teach or suggest a method for protecting a subject against oxidative damage. Hagenfeldt *et al.* also fails to teach or suggest a method for the treatment of amyotrophic lateral sclerosis, Parkinson's disease or Huntington's disease. In addition, Hagenfeldt *et al.* fails to teach or suggest methods using creatine compounds in combination with neuroprotective agents such as inhibitors of glutamate excitotoxicity, mitochondrial cofactors, electron transport chain regulators, spin traps, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcysteine, antioxidants, lipoic acid, cofactors, riboflavin, and CoQ10.

The Applicants' specification is not available as prior art under 35 U.S.C. § 103(a).

Schultheiss *et al.* is directed to a study of the effects of creatine on the synthesis and release of γ-[^{3}H]-aminobutyric acid (GABA) in rat brain slices. Schultheiss found that creatine affects GABA synthesis in rat brain slices. On page 1863, Schultheiss *et al.* teach away from Applicants' invention by stating that "[i]n view of the high concentrations of creatine necessary to obtain these effects, these findings do not have pathophysiological implications."

Schultheiss *et al.* fails to overcome the deficiencies of Hagenfeldt *et al.* Like Hagenfeldt *et al.*, Schultheiss *et al.* also fails to teach or suggest methods using creatine or a creatine kinase modulator in combination with a neuroprotective agent. Furthermore, neither Schultheiss *et al.* not Hagenfeldt *et al.*, alone or in combination, teach or suggest a method for increasing ATP production or protecting a subject from oxidative damage as claimed by Applicants. Neither of the cited reference even mentions oxidative damage or ATP production, let alone a method comprising administering an effective amount of a creatine compound and a neuroprotective agent to protect a subject against oxidative damage or increase ATP production.

Furthermore, Schultheiss *et al.* fails to overcome the deficiencies of Hagenfeldt *et al.* with regards to methods and pharmaceutical compositions for the treatment of amyotrophic lateral sclerosis, Parkinson's disease or Huntington's disease. Both references, alone or in combination, fail to teach or suggest methods or pharmaceutical compositions for the treatment of these diseases. Neither reference teaches nor suggest the particular claimed diseases. Furthermore, there is nothing in Schultheiss *et al.* teach nor suggest that a method for treating MELAS would be broadly applicable to treating other nervous system disorders, such as amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease. In addition, Schultheiss *et al.* fails to overcome the deficiencies of Hagenfeldt *et al.* by also failing to describe the use of administering creatine or creatine compounds in combination with a neuroprotective agent such as inhibitors of glutamate excitotoxicity, mitochondrial cofactors, electron transport chain regulators, spin traps, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcysteine, antioxidants, lipoic acid, cofactors, riboflavin, and CoQ10.

Therefore, Applicant respectfully requests that this rejection of claims 1-4, 6-8, 34-39, 75 and 84-132 under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims 1-4, 6-8, 10-18, 34-39,and 64-132 under 35 U.S.C. § 103(a)

Claims 1-4, 6-8, 10-18, 34-39, and 64-132 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jennings (WO 94/17794).

Applicants claim methods of increasing ATP production of a subject, by administering to the subject an effective amount of a creatine compound and an ATP enhancing agent. Applicants also claim methods of protecting a subject against oxidative damage, by administering to the subject an effective amount of a creatine compound and a neuroprotective agent. In addition, Applicants also claim methods and compositions for the treatment of amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease in a subject. The methods include administering to a subject a therapeutically effective amount of a combination of creatine, a creatine phosphate or a creatine analog and a neuroprotective agent.

Jennings discusses a blend of a glycine derivative, such as creatine, and sugars to enhance tissue formation and as a metabolic supplement. Although the reference alleges that the glycine derivative sugar mixture would be useful for the treatment of multiple sclerosis and dementias, such as Alzheimer's disease, the only examples in Jennings describe the formation of tablets. Furthermore, the reference is silent as to which ingredient is the active ingredient. The examples described by Jennings contain a significant amount of sugar (33% by weight) in combination with creatine. The reference does not teach or suggest that creatine alone or in combination with second agents other than the claimed sugars would be useful for a metabolic supplement or formation of tissue. Furthermore, there is no data or other enabling disclosure which would teach or suggest to an ordinarily skilled artisan that the allegations made by Jennings would be applicable to other disease states or compositions which did not contain the glycine derivative and the sugar, as described.

Jennings does not teach or suggest methods for increasing ATP production, or methods for protecting a subject against oxidative damage by administering a creatine compound and an antioxidant. These methods would not be obvious to the ordinarily skilled artisan because Jennings does not teach or suggest that his compositions would be useful for anything but treating disorders through enhancing tissue formation and increasing metabolism. Jennings does not teach or suggest any methods involving neuroprotection or increasing ATP production as claimed by Applicant.

In addition, Jennings does not teach or suggest methods for the treatment of amyotrophic lateral sclerosis, Parkinson's disease, or Huntington's disease using creatine compounds in combination with inhibitors of glutamate excitotoxicity, mitochondrial cofactors, electron transport chain regulators, spin traps, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcysteine, antioxidants, lipoic acid, cofactors, riboflavin, and CoQ10. In addition, Jennings also fails to teach or describe compositions comprising

neuroprotective agents such as inhibitors of glutamate excitotoxicity, mitochondrial cofactors, electron transport chain regulators, spin traps, growth factors, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, ICE inhibitors, neuroimmunophilis, N-acetylcysteine, antioxidants, lipoic acid, cofactors, riboflavin, and CoQ10, as claimed by Applicants. These combinations would not have been obvious to the ordinarily skilled artisan because there is no teaching in Jennings that would suggest treating the claimed disorders with these specific neuroprotective agents.

Therefore, Applicants respectfully request that this rejection of claims 1-4, 6-8, 10-18, 34-39 and 64-132 under 35 U.S.C. § 103(a), be withdrawn.

SUMMARY

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of/amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the Elizabeth A. Hanley, Esq. at (617) 227-7400.

Date: September 23, 2004

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By _____
Cynthia M. Soroos, Esq.
Reg. No. 53,623
28 State Street
Boston, MA 02109
(617) 227-7400
(617) 742-4214